

Differentiation of Structurally Similar Phenethylamines via Gas Chromatography – Vacuum Ultraviolet Spectroscopy (GC – VUV)

Zackery R. Roberson ^a, John V. Goodpaster ^{a,*}

^a Department of Chemistry and Chemical Biology, Indiana University Purdue University Indianapolis, 402 North Blackford St., LD326, Indianapolis, IN 46202, United States

Corresponding Author

*Address: 402 N. Blackford St., Indianapolis, IN 46202

E-mail: jvgoodpa@iupui.edu

Abstract

The vacuum ultraviolet region includes wavelengths shorter than 200 nm. Electronic transitions of sigma and pi bonds lie in this region, which have the potential to yield structural information. Thus, a VUV detector should be able to detect nearly any molecule analyzable by gas chromatography. This study sought to determine the extent to which structurally similar phenethylamines are differentiated using their VUV spectra. Phenethylamines are a common drug class including pseudoephedrine and illicit drugs such as methamphetamine. Several phenethylamines are difficult to analyze by electron impact mass spectrometry due to their fragmentation giving the same mass to charge ratio fragments at similar ratios. While phenethylamines are generally differentiable by retention time, an extra layer of specificity is preferred in forensic analyses. A Vacuum Ultraviolet (VUV) spectrophotometer coupled to a gas chromatograph was used to collect VUV spectra at high frequency between 125-430 nm. Eight phenethylamines were analyzed for this work using GC/VUV. A calibration curve and limit of detection study was performed that indicates a limit of detection around 10 µg mL⁻¹ and an upper limit of linearity around 1000 µg mL⁻¹. The spectra, analyzed by Principal Component Analysis and Discriminant Analysis, indicate the ability to reliably differentiate each of the drugs from one another including structural isomers and diastereomers. Lastly, five “street” samples containing amphetamines were analyzed to demonstrate “real world” performance.

Key words: GC-VUV, phenethylamines, amphetamines, Vacuum-Ultraviolet, Gas Chromatography, Fast GC

Abbreviations: Vacuum Ultraviolet (VUV), gas chromatography – vacuum ultraviolet spectrophotometry (GC-VUV), infrared detector (IRD), Principal Component Analysis (PCA), linear Discriminant Analysis (DA), n,n-dimethylamphetamine (DMA), n-methylphenethylamine (MPEA), methamphetamine (Meth), amphetamine (Amph), phentermine (Phen), ephedrine (Eph), pseudoephedrine (PE), ethylamphetamine (EA), limit of detection (LOD)

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1. Introduction

Vacuum Ultraviolet (VUV) spectrophotometry coupled to gas chromatography is a relatively new “hyphenated technique” with the ability to differentiate structural isomers and diastereomers. While VUV absorption spectroscopy has been around for many years, the ability to couple VUV spectrophotometry to a separation technique is a recent development.[1] The region of the electromagnetic spectrum known as the vacuum ultraviolet extends to wavelengths shorter than 200 nm where the electronic transitions of sigma and high energy pi bonds lie. The detector used for this study has a spectral range of 125-430 nm, where all but the smallest molecule (H_2) absorbs. With nearly every molecule absorbing in this region, the question arises as to just how differentiable these spectra are? This study seeks to determine the discriminating power of this technique through chemometrics.

Chemometrics is multivariate statistics applied to chemistry to extract valuable information from a data set. [2-5] Of the many statistical methods available, Principal Component Analysis (PCA) and Discriminant Analysis (DA) were used for this study. PCA was chosen for its ability to show correlations in a data set as an unsupervised technique. DA was used for its ability to separate the different groups within the data set as a supervised technique. Using PCA and DA, the spectra of the phenethylamines were analyzed and determined to be sufficiently differentiable from one another.

In forensic chemistry, several phenethylamines are commonly found in seized drug exhibits (see Figure 1). Five seized drug casework samples, de-identified from the Indiana State Police, were analyzed as “street” samples for his work. In general, phenethylamines when analyzed by GC-MS, while distinguishable by gas chromatography and retention time, give fragments with the same mass to charge ratio and in similar ratios of fragments as other phenethylamines. Methamphetamine’s fragmentation has been studied in detail [6] but is also known to be sufficiently similar to its stereoisomers and regioisomers to make definitive identification difficult with fragment ions at m/z 58 and m/z 91 being predominant. [7] GC-IRD (infrared detector) has been proposed as a possible complimentary technique to differentiate these isomers. [7] Though the spectra can be more visually distinct with an IRD, VUV is more sensitive and allows for easier quantitation.[8] Having the same functional groups, the seven phenethylamines studied in this work would have similar spectra in both the IR and VUV regions. Where IR detection relies on vibrational modes of the functional groups on a molecule, VUV is dependent on the electronic transitions of the molecule. Both techniques are affected by vibronic coupling that allows for spectra to be potentially unique to each molecule. The phenethylamines in this study, though similar in spectra, produce individual spectra that allow for the identification of one apart from another.

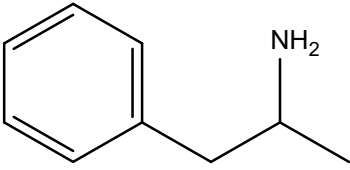
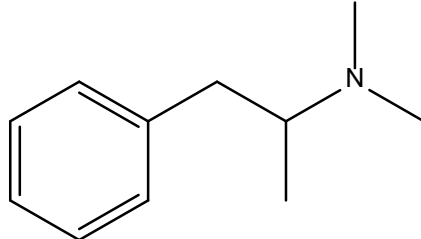
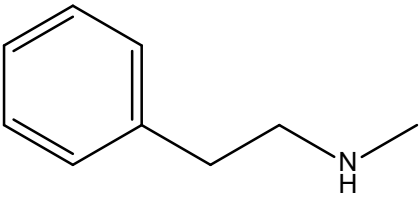
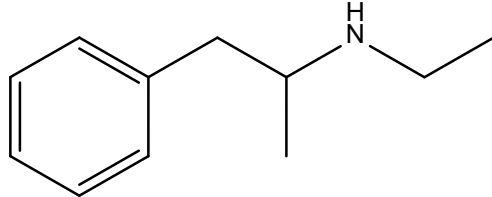
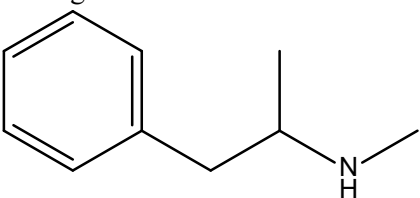
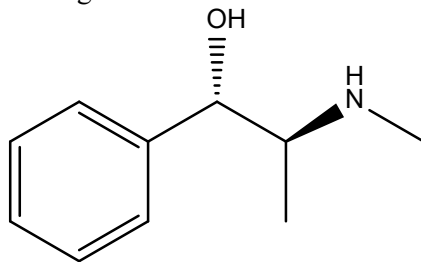
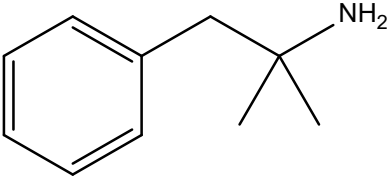
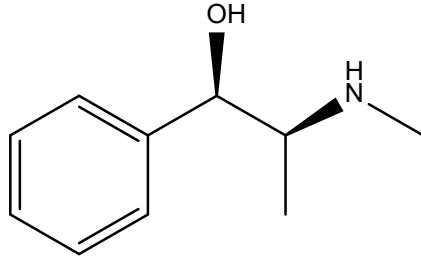
Amphetamine 135.2 g mol^{-1} 	n,n-dimethylamphetamine 163.3 g mol^{-1} 
n-methylphenethylamine 135.2 g mol^{-1} 	Ethylamphetamine 163.3 g mol^{-1} 
Methamphetamine 149.2 g mol^{-1} 	Ephedrine 165.2 g mol^{-1} 
Phentermine 149.2 g mol^{-1} 	Pseudoephedrine 165.2 g mol^{-1} 

Figure 1: Structures and molar masses of the phenylethylamines discussed in this work.

VUV's specificity has been increasingly demonstrated since its availability on the market beginning in 2014. VUV has also been used in tandem with MS.[9] VUV has shown the ability to differentiate fatty acid methyl esters, pesticides, fuels, and more. [1, 10-18] VUV has been demonstrated to be able to differentiate 67 designer drugs.[10, 19-21].

One of the exciting advantages of VUV is the ability to easily quantify as well as characterize an analyte. VUV is reliant on the Beer-Lambert Law for quantification and has been considered as a pseudo-absolute quantitation method.[22] With the reliance on Beer's Law, VUV is a

concentration dependent detector, though mass dependent characteristics such as increased sensitivity with an increased flow rate through the instrument are observed.[23]

2. Materials/Methods

2.1 Materials. Methylene chloride was purchased from Fisher Scientific (Fairlawn, NJ) for solution preparation and dilution. All vials and caps were purchased from Fisher Scientific as well. D-amphetamine, N,N-DMA (dimethylamphetamine), and ethylamphetamine were purchased from Cayman Chemical (Ann Arbor, MI). Phentermine HCl was obtained from USP (Rockville, MD). Methamphetamine, ephedrine, and s,s-pseudoephedrine were purchased from Sigma-Aldrich (St Louis, MO). N-Methylphenethylamine (MPEA) was obtained from Acros Organics (China).

2.2 Instrumentation. An Agilent 7890A gas chromatograph with 7693 autosampler was connected to a VUV Analytics VGA-101 Vacuum Ultraviolet spectrophotometer. This instrument was used to obtain all chromatographic and spectrophotometric data. All liquid injection vials and caps were purchased from Fisher Scientific (Hanover Park, IL).

2.3 Gas Chromatography Method for drug analysis. A flow of 1.8 mL min^{-1} of hydrogen was used for the carrier gas, inlet temperature 250°C , injection volume $1 \mu\text{L}$ (splitless), oven ramped from 50°C to 250°C at a rate of $20^\circ\text{C min}^{-1}$ with a final oven temperature hold of 2.50 minutes. The VGA-101 transfer line and flow cell were set to a temperature of 275°C and a makeup gas pressure of 0.35 psi of nitrogen. The VGA-101 was set to a sampling rate of 6 Hz.

2.4 Chemometric Analysis. The phenethylamine spectra were baselined subtracted and the absorbance was normalized to the square root of sum of squares of all wavelengths. The software used for the multivariate analyses was JMP 13 by SAS Institute.

2.5 Determination of Figures of Merit. Accuracy and precision determined by analysis of five calibrants and a separate challenge sample, all TFAA derivatized MPEA in triplicate. Calibrants were prepared at 180, 150, 100, 50, and $25 \mu\text{g mL}^{-1}$, the challenge samples were prepared at $75 \mu\text{g mL}^{-1}$ in a manner identical to the calibrants from a separate stock. LOD and linearity were determined with triplicate calibrants spanning the range from $10 \mu\text{g mL}^{-1}$ to $1000 \mu\text{g mL}^{-1}$.

3. Results/Discussion

3.1 GC/VUV Analysis

Solutions of seven phenethylamines (methamphetamine, amphetamine, methylphenethylamine, phentermine, dimethylamphetamine, ethylamphetamine, and pseudoephedrine) were prepared at 0.5 mg mL^{-1} and a solution of ephedrine was prepared at 1.4 mg mL^{-1} . All standard solutions were analyzed by GC-VUV.

The separation of seven phenethylamines can be seen in the chromatogram in Figure 2. Ephedrine was excluded because it could not be well resolved from pseudoephedrine. Tailing of peaks is common for underivatized phenethylamines on a column with a silicone stationary phase due to the basic nature of the molecules.

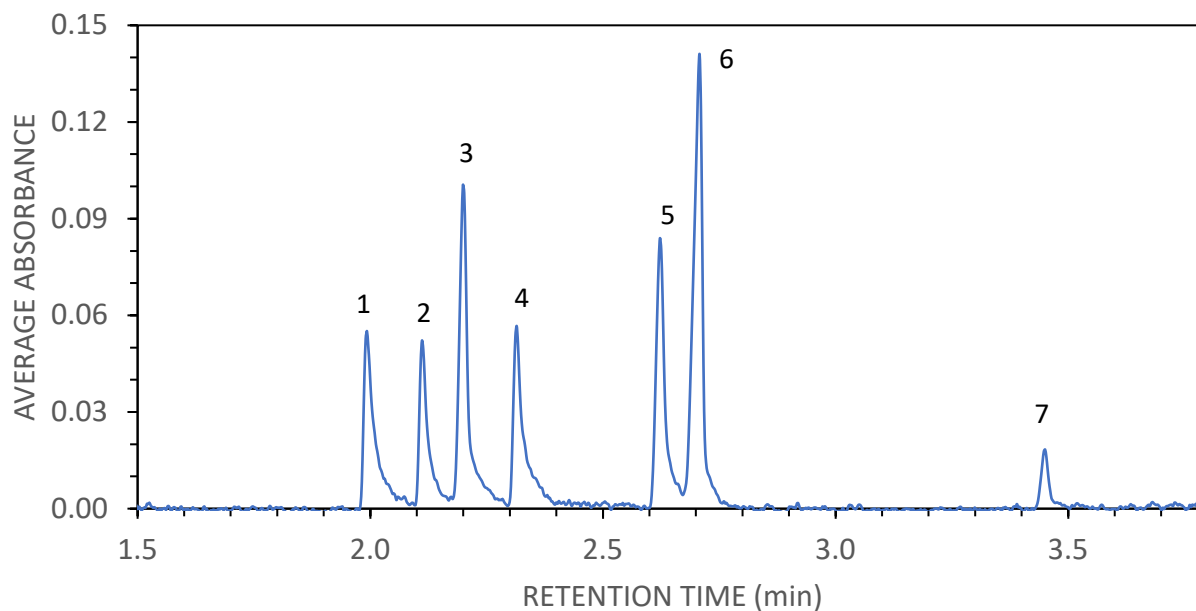


Figure 2: Chromatogram of seven phenethylamines. Peaks: 1) amphetamine, 2), MPEA, 3) phentermine, 4) methamphetamine, 5) ethylamphetamine, 6) DMA, 7) pseudoephedrine.

The normalized and overlaid spectra are shown in Figure 3. The spectra are rather similar with all having a decreasing “slope” of absorbance from <125 nm, absorbance maxima around 185 nm, and a “shoulder” around 210 nm.

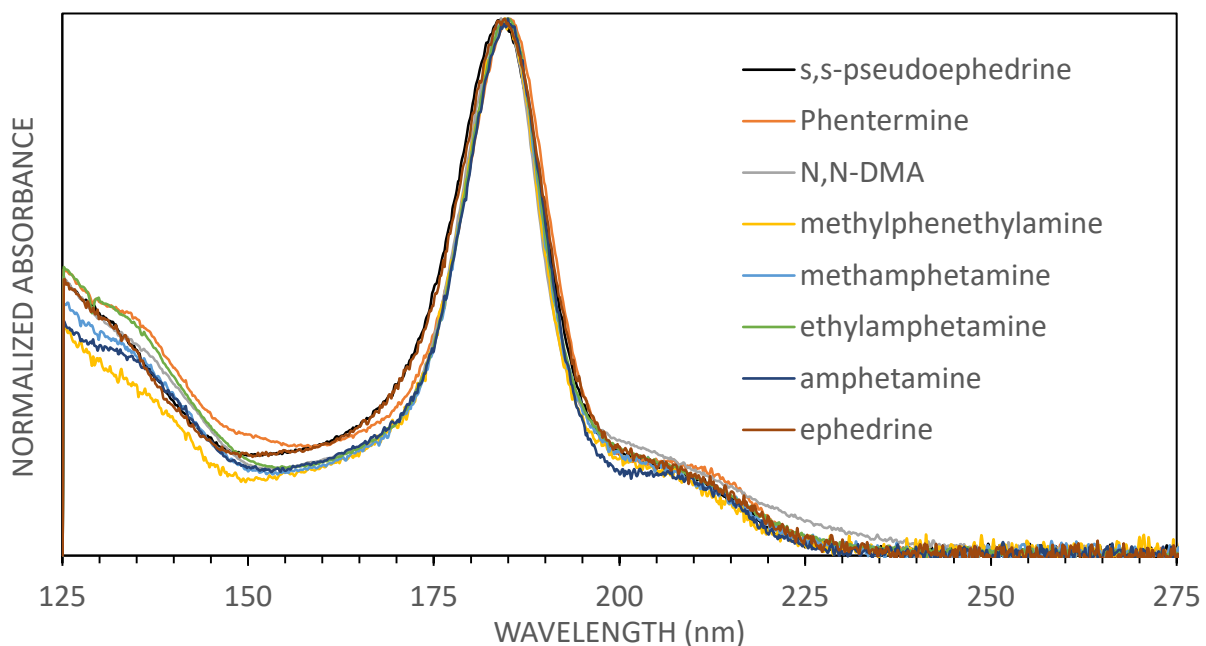


Figure 3: Overlaid spectra of S,S-pseudoephedrine, phentermine, dimethylamphetamine (N,N-DMA), methylphenethylamine, methamphetamine, ethylamphetamine, amphetamine, and ephedrine. The spectra were truncated at 275 nm because no sample absorbed at longer wavelengths.

3.2 Assessing Similarity/Dissimilarity of Spectra

The average correlation coefficients and sums of square residuals provide numeric values for the similarity of the spectra as seen in Table 1.

SSR COR	PE	Eph	Amph	MPEA	Meth	Phen	DMA	EA
PE	0.0377 0.9997	0.3734	1.3324	1.8717	1.0488	1.1414	1.1167	1.0869
Eph	0.9973	0.0152 0.9999	1.5427	2.1568	1.2495	1.1249	1.3806	1.2569
Amph	0.9944	0.9936	0.1000 0.9992	0.5404	0.2650	1.3978	0.9721	0.8669
MPEA	0.9933	0.9921	0.9960	0.1329 0.9989	0.6764	2.9698	1.4793	1.8467
Meth	0.9947	0.9938	0.9979	0.9960	0.0650 0.9995	1.1701	0.4607	0.4349
Phen	0.9916	0.9916	0.9945	0.9865	0.9949	0.0256 0.9998	1.2290	0.5798
DMA	0.9932	0.9914	0.9942	0.9927	0.9975	0.9924	0.0330 0.9997	0.3414
EA	0.9923	0.9913	0.9951	0.9902	0.9977	0.9966	0.9976	0.0282 0.9998

Table 1: Matrix of correlation coefficients (COR) and sums of square residuals (SSR) for the phenethylamines pseudoephedrine (PE), ephedrine (Eph), amphetamine (amph), MPEA, methamphetamine (Meth), phentermine (Phen), DMA, and ethylamphetamine (EA). Sums of square residuals are given in red whereas correlation coefficients are given in blue. Averages taken from three by three matrices of triplicates.

To the extent that SSR for two analytes approaches zero or r approaches unity, deconvolution of a chromatographic peak containing the two analytes becomes increasingly difficult. Given that SSR is a continuous variable with a lower limit of 0 and no upper limit, it can vary significantly within a group of compounds. In general, pairs of co-eluting compounds with $SSR > 1$ can be deconvoluted using the VUV software. Classes of compounds from previous publications in the area of GC/VUV are summarized in Table 2 with a comparison to the SSR results from this study.

Analytes	n	SSR range	Ref.
Designer Drugs (methcathinones)	43	1 - 227	[24]
Dimethylnaphthalene isomers	8	0.60 – 42.65	[8]
Benzene isotopologes	10	0.0158 – 1.70	[25]
Phenylethylamines	8	0.158 – 3.225	This Work

Table 2 Comparison of the sums of square residuals (SSR) for various compound classes as compared to this work. The SSR of a compound spectrum compared to itself is zero.

The use of multi-variate statistical methods applied to chemical data (chemometrics) were also explored. After normalization, the spectral data was analyzed by Principal Components Analysis (PCA). The PCA results are shown in Figure 4. The spectra of the phenethylamines produced distinct groups with little variation between replicates. Two outliers can be seen in the score plot, one being a replicate of DMA and one a replicate of ephedrine.

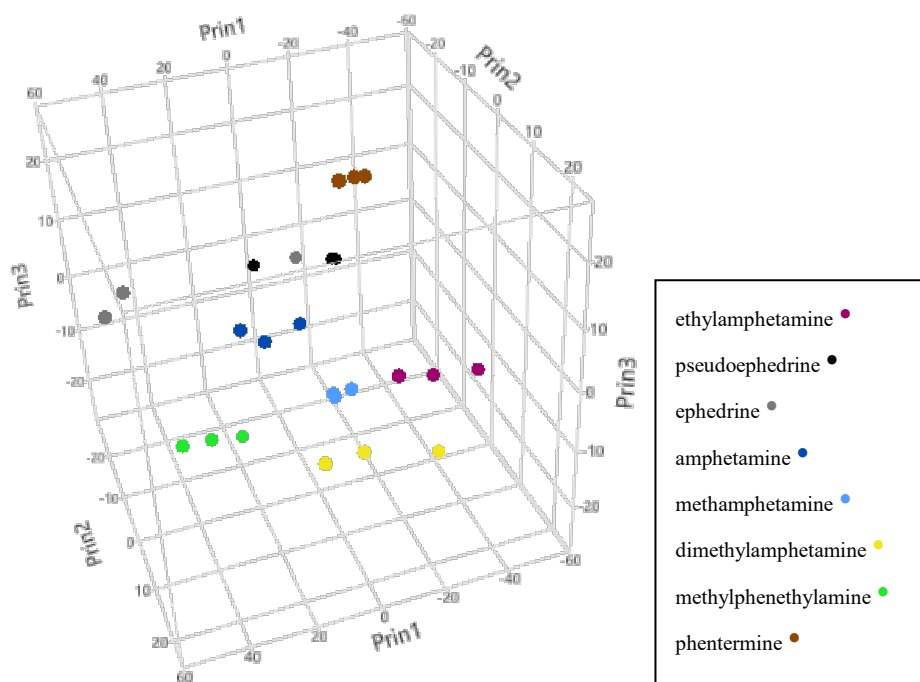


Figure 4: 3-dimensional PCA scores plot of Principle Components (Prin1, Prin2, and Prin3) showing the distribution of the phenethylamines based on their VUV spectra..

The first 4 principal components, representing 91.8% of the cumulative variance, were subjected to DA with the categories being the seven phenethylamines. Clear distinction was observed between six of the eight phenethylamines. Ephedrine and pseudoephedrine clustered close together but are still distinguishable. The DA results are shown in Figure 5.

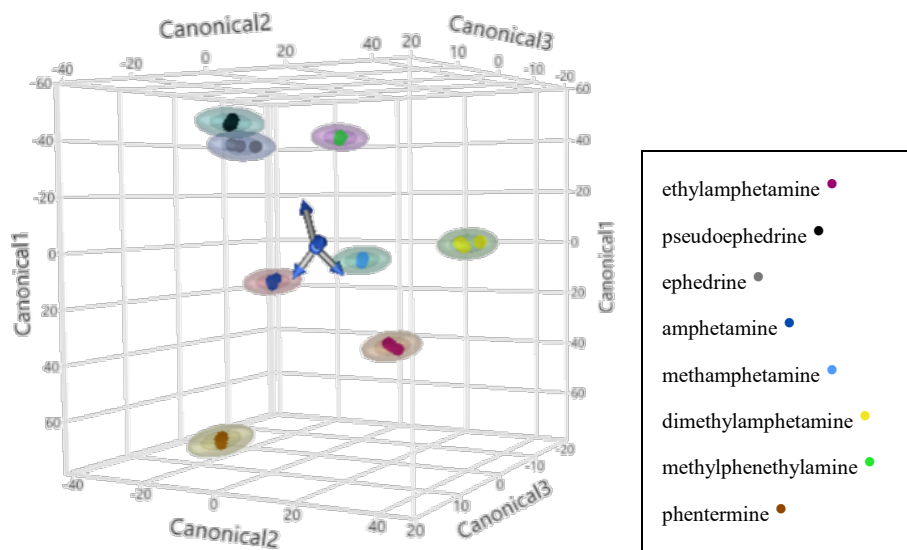


Figure 5: Three-dimensional canonical plot illustrating the clustering of the phenethylamines. The ellipsoids indicate the 95% confidence interval for each compound class. The first four principle components were used as inputs for the DA.

3.3 Differentiating Ephedrine and Pseudoephedrine

Given their nearly identical structure, the diastereomers Ephedrine and Pseudoephedrine were analyzed in greater detail. In particular, the correlation coefficients for the ephedrine and pseudoephedrine replicates (see Table 1) were Fisher transformed and found to be statistically significant via the “student’s T-test” at a 95% confidence interval.

Seven replicates of pseudoephedrine and ephedrine were analyzed to determine if the diastereomers were reliably differentiable. Visual spectral comparison is given in Figure 6 with a magnified view of the maxima. A very slight blue shift in the pseudoephedrine spectra can be observed at both ends of the maximum. Both compounds overlap at the 184 nm maxima, in the “valley” between 150-155 nm, and approaching 125 nm.

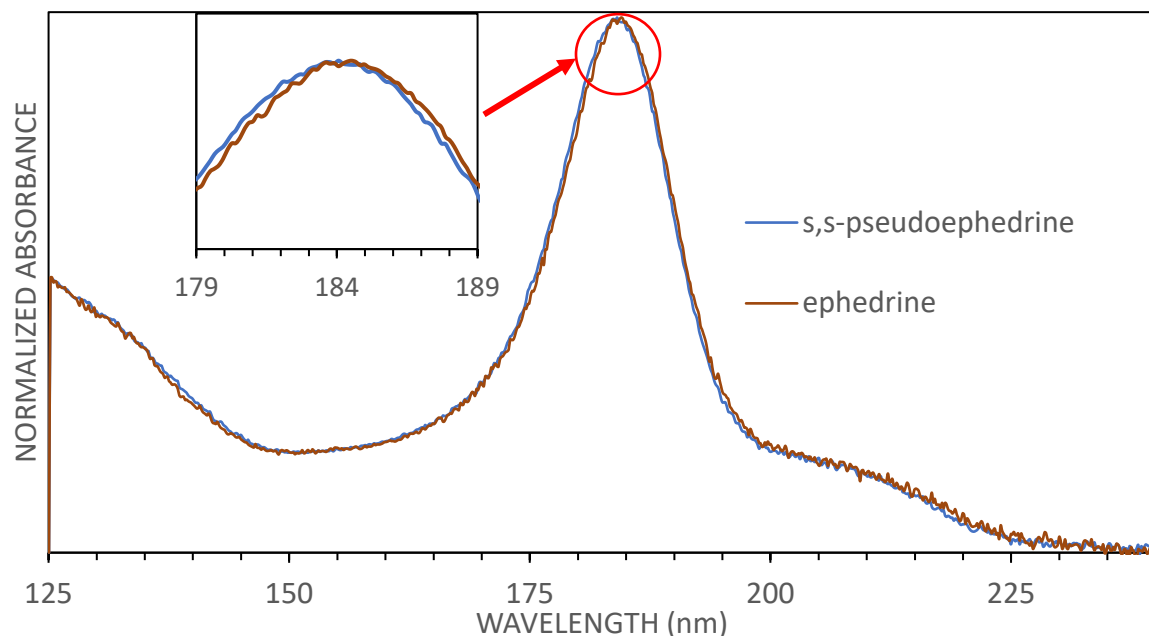


Figure 6: Overlaid spectra of S,S-pseudoephedrine and ephedrine, spectra were truncated at 240 nm as neither absorbed at longer wavelengths. Window magnifying the region between 179 and 189 nm highlighting the blue shift of the pseudoephedrine.

The normalized diastereomer data was analyzed by PCA which separated the ephedrine and pseudoephedrine samples along Component 2. The two-dimensional PCA is given in Figure 7A. The first 4 principle components were then analyzed by DA resulting in Figure 7B. For the DA, 4 replicates of each compound were used for the training set and 3 replicates were used as the training set, the classification accuracy was found to be 100%.

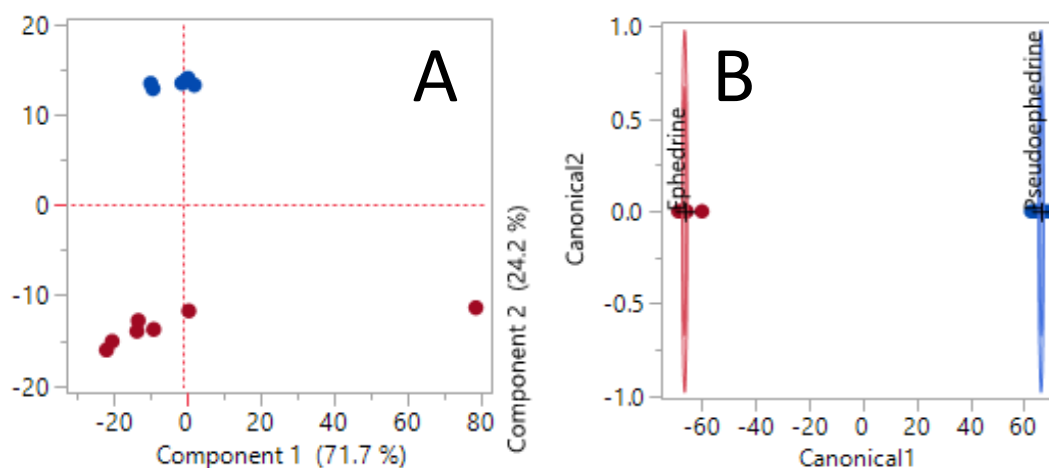


Figure 7: A) 2-dimensional score plot showing the distribution of ephedrine and pseudoephedrine along Component 2 B) 2-dimensional canonical plot showing the classification and 95% confidence interval around ephedrine and pseudoephedrine. The first four principle components were inputs for the DA.

Based on the spectral differences and chemometric differentiation, diastereomers such as ephedrine and pseudoephedrine are differentiable by VUV Spectrophotometry. Differentiation of diastereomers is impossible by Mass Spectrometry, though chromatography can be used to separate and distinguish diastereomers.

3.4 Figures of Merit and Comparison to GC/MS

The phenethylamines were also analyzed by GC-MS using a method that is in common use by forensic chemists. The three most abundant m/z fragments for each compound are tabulated in Table 3 with relative abundances. Relative abundances will vary slightly from instrument to instrument, limiting the ability to make determinations based on relative abundances. [26] Ephedrine was excluded as it is a diastereomer of pseudoephedrine and would give the same mass spectrum despite having a slightly different retention time and VUV spectrum.

	Amph	MPEA	Phen	Meth	PE	EA	DMA
Base Peak (m/z)	44 (100%)	44 (100%)	58 (100%)	58 (100%)	58 (100%)	72 (100%)	72 (100%)
2 nd (m/z)	91 (55%)	91 (42%)	91 (33%)	91 (29%)	77 (22%)	91 (28%)	91 (16%)
3 rd (m/z)	65 (16%)	65 (13%)	134 (20%)	134 (7%)	105 (17%)	44 (9%)	65 (5%)

Table 3: The three most abundant fragment ions for amphetamine (Amph), MPEA, phentermine (Phen), methamphetamine (Meth), pseudoephedrine (PE), ethylamphetamine (EA), and DMA with the relative abundance to the base peak in the corresponding mass spectrum.

A GC/VUV LOD study using MPEA as a phenethylamine exemplar determined the LOD to be 10 ng on column. The method for determining LOD used peak height from a spectral filter summing the absorbance from 184 nm to 185 nm. Peak area results from the LOD analyses indicated a lower limit of linearity of 25 ng on column and an upper limit of linearity around 1 μg on column with an R^2 of 0.9971 for the mentioned range. It is possible that with further method development the LOD could reach 1 ng on column or lower. The linearity and LOD determinations were compared to that of an MSD in “scan” mode, the values obtained from the extracted ion chromatograms for the base peak at m/z 44 produced similar LOD results to the VUV. If the MSD had been operated in the “SIM” mode the LOD and linearity limits would decrease by at least an order of magnitude.

An accuracy and precision study using the derivatized form of MPEA was conducted at concentrations ranging from 180 to 25 $\mu\text{g ml}^{-1}$, the derivative was used to improve precision from one analysis to another. The spectra of MPEA and the TFAA derivative of MPEA are shown in Figure 8. An obtained average percent error of -0.26% and relative standard deviation of 0.62% were determined from calculating the concentration of a challenge sample prepared in identical manner to the calibration samples but from a separate stock and at a concentration bracketed by, but separate from, the calibrants. It is suspected that the derivatized form would lower LODs below 10 ng on column. Pre-concentration techniques or more sensitive methods are recommended for future work.

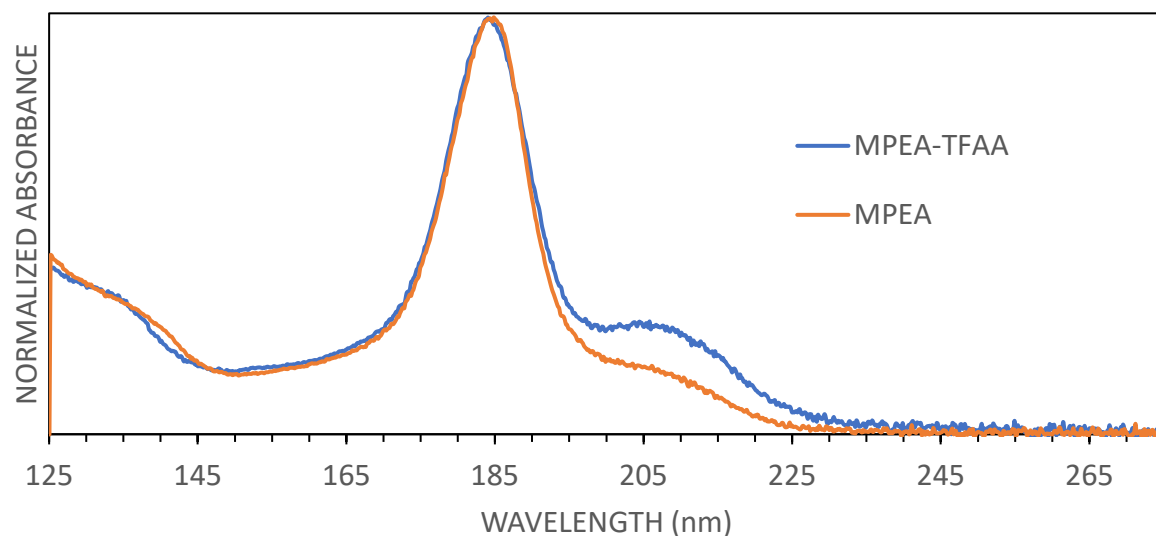


Figure 8: Overlaid spectra of MPEA non-derivatized and MPEA-TFAA derivative.

Upon derivatization the absorbance spectrum alters from the non-derivatized form by shifting in the sigma bond region from 125-150 nm, an observed hypsochromic shift in the maximum, and a larger absorbance band is seen from 190-235 nm in the pi bond region.

3.5 “Real World” Samples

Five “street” samples of seized phenethylamine exhibits were analyzed by GC-VUV. GC-MS analysis performed for comparison. The chromatograms from the GC-VUV analyses are in Figure 9.

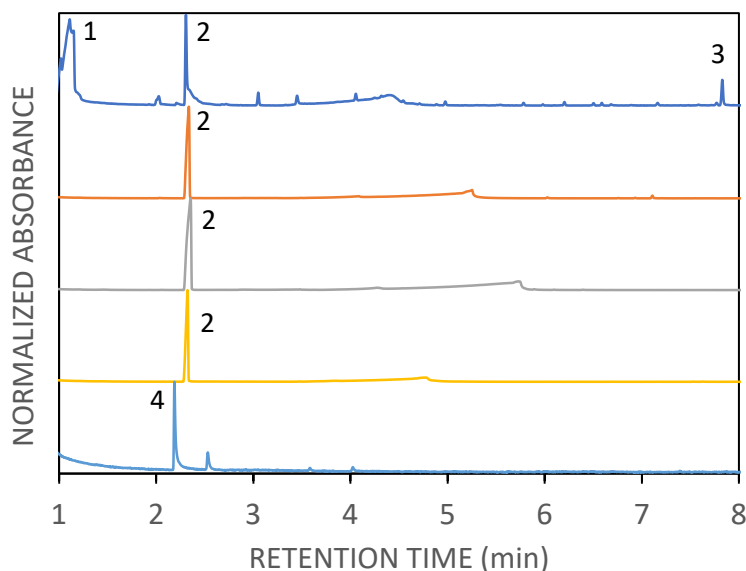


Figure 9: Seized “street” samples of phenethylamines. Peaks: 1) dimethyl sulfone, 2) methamphetamine, 3) cocaine, 4) phentermine.

The peaks labeled in Figure 9 were consistent with the standards analyzed. There are unidentified peaks in the top trace for which the limited library could not identify and was not consistent with any standards analyzed in this work. Future work is needed to expand on the available VUV spectra of compounds to contribute to a spectral library that can be used for reference.

4. Conclusions

Several forensically-important phenethylamines were analyzed by GC-VUV and found to be distinguishable from one another. The diastereomers ephedrine and pseudoephedrine are distinguishable by VUV spectrophotometry. The specificity of the VUV absorbance spectra was further supported by chemometric analyses. A limit of detection of 10 ng on-column was determined for methylphenethylamine and is representative of the eight phenethylamines. Though GC-MS analysis gives results that can be ambiguous for certain phenethylamines, GC-VUV with chemometrics shows unambiguous discrimination for these compounds. Ephedrine and pseudoephedrine can also be discriminated despite being diastereomers. We consider GC-VUV to be an excellent complimentary technique to GC-MS and would do well in forensic labs.

5. Acknowledgements

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